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Novel combination of loteprednol and antihistamines

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The present invention relates to a novel combination of
 5 a soft steroid, in particular loteprednol, and at least
 one antihistamine, such as, for example, azelastine
 and/or levocabastine, for simultaneous, sequential or
 separate administration in the local treatment of
 allergies and airway disorders, for example of allergic
 10 rhinitis (rhinoconjunctivitis).

Background of the invention

The number of allergic disorders is increasing greatly
 15 worldwide. Studies have shown that on average 7.5% of
 all children and adolescents worldwide suffer from
 rhinoconjunctivitis (hay fever combined with an ocular
 symptomatology) (Worldwide variation in prevalence of
 symptoms of asthma, allergic rhinoconjunctivitis and
 20 atopic eczema: ISAAC, Lancet, 351, 1225-1332, 1998). In
 West European countries, the prevalence, at about 14%,
 is markedly higher (Annesi-Maesano I. and Oryszczyn
 MP.: Rhinitis in adolescents, Results of the ISAAC
 survey, Revue Française d'Allergologie et d'Immunologie
 25 Clinique, 38, 283-289, 1998; Norrman E., Nystrom L,
 Jonsson E and Stjernberg N: Prevalence and incidence of
 asthma and rhinoconjunctivitis in Swedish teenagers,
 European Journal of Allergy and Clinical Immunology,
 53, 28-35, 1998). Despite intensive research activity,
 30 the pathogenesis of rhinoconjunctivitis has still not
 been completely clarified. Even if marked advances in
 the medicinal treatment of this disorder have been
 achieved in the past years, the therapy is still not
 satisfactory. The acute symptoms (itching, reddening,
 35 swelling, rhinorrhea and lacrimation) of
 rhinoconjunctivitis can be readily controlled, inter
 alia with the aid of antihistamines. However, they
 barely have a therapeutically relevant influence on the
 inflammation which underlies the disorder and is always

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dynamically active substance reaches the systemic blood circulation, so that the steroid-specific side effects virtually do not have to be reckoned with. Loteprednol is already licensed for the therapy of allergic
5 conjunctivitis and uveitis.

Antihistamines are employed in the acute phase of allergic rhinoconjunctivitis for the alleviation of the often irritating symptoms. The topical application of
10 these medicaments is particularly advantageous, as high local concentrations of the active compound can be broken down in this way without having to reckon with appreciable side effects. At the current time, two locally administrable antihistamines, azelastine and
15 levocabastine, are on the market. Both are highly efficacious and very highly tolerable.

Surprisingly, it has now been found that the novel combination of a soft steroid and at least one
20 antihistamine is advantageous in the treatment of allergies and/or airway disorders by topical administration. Administration can in this case be carried out simultaneously, sequentially or separately. The invention serves to improve the therapy of allergic
25 rhinitis (rhinoconjunctivitis). The antihistamine provides for the rapid elimination of the acute symptoms (e.g. reddening, itching, swelling). Using the corticosteroid contained in the combination, the inflammation underlying the condition can be
30 successfully controlled.

According to one embodiment of the invention, loteprednol and its pharmaceutically acceptable esters, in particular loteprednol etabonate, is a particularly
35 suitable soft steroid. The preparation of loteprednol and loteprednol etabonate is described, for example, in German Patent No. DE 31 26 732, the corresponding US Patent No. 4,996,335 and the corresponding Japanese Patent No. JP-89 011 037.

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According to a further embodiment of the invention, the antihistamine can also be administered orally.

The intended dosage is carried out twice daily, the individual dose of the soft steroid (loteprednol) being between 10 and 500 µg, preferably 50 and 200 µg. The dose of antihistamine is 50 - 500 µg, preferably 100 - 200 µg. The actual dose depends on the general condition of the patients (age, weight, etc.) and the degree of severity of the disorder.

The following pharmacological investigation was carried out in order to support the invention described.

In vitro, investigations on the influencing of the release of the proinflammatory cytokine TNFα in human blood of various donors diluted 1:5 were carried out. The stimulation was effected using lipopolysaccharide (LPS) from Salmonella abortus equi (10 µg/ml) over the course of 24 h at 37°C and 5% CO₂ in an incubator. The TNFα release was determined using an ELISA, based on antibodies from Pharmingen. The results were indicated as the percentage inhibition of the LPS-induced TNFα release and are shown in Table 1.

Table 1

Active compound	Concentration [µmol/l]	Inhibition of TNFα release
Azelastine	10	2%
Loteprednol	0.001	1%
	0.01	2%
	0.03	8%
Azelastine + loteprednol	10 + 0.001	12%*
	10 + 0.01	18%*
	10 + 0.03	22%*

* significant (p<0.05)

If the antihistamine azelastine or the soft steroid loteprednol is administered alone, the LPS-induced TNFα

release remains virtually unchanged. In the presence of azelastine (10 $\mu\text{mol/l}$) the TNF α release is inhibited to an increased extent by loteprednol in a concentration-dependent manner.

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In vivo investigations were carried out on young domestic pigs actively sensitized with an antigen (extract from *Ascaris suum*). Three weeks later, they were exposed to allergen challenge, which was carried out by intranasal instillation of the *Ascaris* extract. This local intranasal allergen challenge leads to a very great increase in the nasal secretion (rhinorrhea). The amount of secretion was determined gravimetrically. The results are compiled in Table 2.

10

15 Table 2

Active compound	Dose in $\mu\text{g/nosril}$	Inhibition of nasal secretion	Number of animals
Azelastine	10	15%	5
Loteprednol	20	8%	5
Azelastine + loteprednol	10 + 20	48%*	5

* significant ($p < 0.05$)

20 If the antihistamine azelastine or the soft steroid loteprednol is used at the dosages 10 or 20 $\mu\text{g/nosril}$, only marginal inhibition of the allergically induced nasal hypersecretion occurs. If both active compounds are given at the same time, however, the rhinorrhoea is 25 (significantly) reduced by 48%.

Various pharmaceutical formulations, e.g. nasal sprays, nasal drops and eye drops, are suitable for topical application.

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The present invention describes a combination in which a soft steroid, e.g. loteprednol, and an antihistamine, e.g. azelastine and/or levocabastine, are administered

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simultaneously, one after the other as individual substances or as a fixed combination.

On account of the water solubility of the active compound azelastine hydrochloride, formulations containing this active compound can preferably be formulated as solutions. Loteprednol etabonate, however, is virtually water-insoluble and is therefore formulated as an aqueous suspension. In a formulation in which both active compounds are combined, azelastine hydrochloride is accordingly present dissolved in water and loteprednol etabonate suspended in water.

In addition to the active constituents antihistamine, e.g. azelastine hydrochloride, and soft steroid, e.g. loteprednol etabonate, the pharmaceutical preparations according to the invention can contain further constituents such as preservatives, stabilizers, isotonicizing agents, thickeners, suspension stabilizers, excipients for pH adjustment, buffer systems and wetting agents.

Examples of suitable preservatives are: benzalkonium chloride, chlorobutanol, thiomersal, methylparaben, propylparaben, sorbic acid and its salts, sodium edetate, phenylethyl alcohol, chlorhexidine hydrochloride acetate and digluconate, cetylpyridinium chloride and bromide, chlorocresol, phenylmercury acetate, phenylmercury nitrate, phenylmercury borate, phenoxyethanol.

For preservation, the combination of sodium edetate and benzalkonium chloride is preferably used. Sodium edetate is employed here in concentrations of 0.05 - 0.1% and benzalkonium chloride in concentrations of 0.005 - 0.05%. The combination of sodium edetate, benzalkonium chloride and phenylethyl alcohol is also preferably employed.

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Suitable excipients for the adjustment of the isotonicity of the formulations are, for example: sodium chloride, potassium chloride, mannitol, glucose, sorbitol, glycerol, propylene glycol. In general, these
5 excipients are employed in concentrations from 0.1 to 10%.

The formulations of the invention can also include suitable buffer systems or other excipients for pH
10 adjustment in order to establish and maintain a pH of the order of magnitude of 4-8, preferably of 5 to 7.5. Suitable buffer systems are citrate, phosphate, tromethamol glycine, borate, acetate. These buffer systems can be prepared from substances such as,
15 citric acid, monosodium phosphate, disodium phosphate, glycine, boric acid, sodium tetraborate, acetic acid, sodium acetate,
Further excipients can also be used for pH adjustment, such as hydrochloric acid or sodium hydroxide.

20 In order to prepare a stable aqueous suspension containing the water-insoluble active compound loteprednol etabonate, suitable suspension stabilizers and suitable wetting agents are furthermore necessary
25 in order to disperse and to stabilize the suspended active compound in a suitable manner.

Suitable suspension stabilizers are water-soluble or partly water-soluble polymers: these include, for
30 example, methylcellulose (MC), sodium carboxymethylcellulose (Na-CMC), hydroxypropylmethylcellulose (HPMC) polyvinyl alcohol (PVAL [sic]), polyvinylpyrrolidone (PVP), polyacrylic acid, polyacrylamide, gellan gum (Gelrite®) hydrated alumina (Unemul®) dextrans,
35 cyclodextrins, and mixtures of Microcrystalline cellulose and sodium carboxymethylcellulose (Avicel RC 501®, Avicel RC 581®, Avicel RC 591®, Avicel CL 611®). These substances can simultaneously serve as thickeners in order to increase the viscosity and thereby to

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prolong the contact of the active compounds with the tissue at the application site.

Suitable wetting agents for the formulations are:

- 5 benzalkonium chloride, cetylpyridinium chloride, tyloxapol, various polysorbates (Tween®), and further polyethoxylated substances and poloxamers.

Examples:

- 10 The following examples illustrate the invention without restricting it.

Example 1:

Nasal spray containing azelastine hydrochloride (0.1%)

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Azelastine hydrochloride	0.1000 g
Hydroxypropylmethylcellulose	0.1000 g
Sodium edetate	0.0500 g
Benzalkonium chloride	0.0125 g
Sodium hydroxyde	q.s. ph 6.0
Sorbitol solution 70%	6.6666 g
Purified water	to 100 ml

Preparation of the solution:

- 20 Introduce about 45 kg of purified water into a suitable stirrer container. Add the active compound, hydroxypropylmethylcellulose, sodium edetate, benzalkonium chloride and sorbitol solution to this in succession and dissolve with stirring. Make up the resulting solution to a volume of 49.5 liters with
- 25 purified water. Adjust the pH of the solution to pH 6.0 using 1N sodium hydroxide solution. Make up to the final volume of 50.0 liters using purified water and Stir. Filter the solution through a suitable filter and dispense into bottles which are then provided with a
- 30 suitable nasal spray pump.

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Example 2:

Nasal spray suspension containing loteprednol etabonate
(1%)

Loteprednol etabonate	1.0000 g
Avicel RC 591	1.1000 g
Polysorbate 80	0.1000 g
Sorbitol solution 70%	6.0000 g
Sodium edetate	0.0500 g
Benzalkonium chloride	0.0200 g
Purified water	to 100 ml

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Preparation:

Introduce 45 kg of purified water into a suitable
stirrer container with a homogenization device and
10 homogenize Avicel RC 591 therein at high speed. Then
dissolve the substances polysorbate 80, sorbitol
solution, sodium edetate and benzalkonium chloride in
succession with stirring. Then homogenize the active
compound loteprednol etabonate at high speed until a
15 uniform suspension is formed. Then make up to the final
volume of 50 liters with purified water and homogenize
further. Then evacuate the suspension in order to
remove the resulting air bubbles. The resulting
suspension is then dispensed into bottles which are
20 then provided with a suitable nasal spray pump.

Example 3:

Nasal spray containing loteprednol etabonate (1%,
suspended) and azelastine hydrochloride (0.1%,
25 dissolved)

Loteprednol etabonate	1.0000 g
Azelastine hydrochloride	0.1000 g
Avicel RC 591	1.1000 g
Polysorbate 80	0.1000 g
Sorbitol solution 70%	6.0000 g
Sodium edetate	0.0500 g
Benzalkonium chloride	0.0200 g
Purified water	to 100 ml

Preparation:

5 Introduce 45 kg of purified water into a suitable stirrer container with a homogenization device and homogenize Avicel RC 591 therein at high speed. Then dissolve the active compound azelastine hydrochloride and the excipients polysorbate 80, sorbitol solution,
 10 sodium edetate and benzalkonium chloride in succession with stirring.

Then homogenize the active compound loteprednol etabonate at high speed until a uniform suspension is formed. Then make up to the final volume of 50 liters
 15 with purified water and homogenize further. Then evacuate the suspension in order to remove the resulting air bubbles.

The resulting suspension is then dispensed into bottles which are then provided with a suitable nasal spray
 20 pump.